PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 26 JUL 2005
WIPO PCT

Applicant's or agent's file reference 4-33146A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/003418	International filing date *(day/month/year)* 31.03.2004	Priority date *(day/month/year)* 01.04.2003
International Patent Classification (IPC) or national classification and IPC A61K31/55, A61P25/14		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.10.2004	25.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Büttner, U Telephone No. +49 89 2399-7841

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003418

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-7 as originally filed

   Claims, Numbers

   1-12 filed with telefax on 02.11.2004

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003418

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 5-8 (with regard to Industrial Applicability)

because:

☒ the said international application, or the said claims Nos. 5-8 (with regard to Industrial Applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-4, 9-12
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 5-8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.) Reference is made to the following documents:

D1: AMBROSIO A F ET AL: "MECHANISMS OF ACTION OF CARBAMAZEPINE AND ITS DERIVATIVES, OXCARBAZEPINE, BIA 2-093, AND BIA 2-024" NEUROCHEMICAL RESEARCH, PLENUM PRESS, NEW YORK, US, vol. 27, no. ½, February 2002 (2002-02), pages 121-130, XP009022844 ISSN: 0364-3190

D2: BENES J ET AL: "Anticonvulsant and Sodium Channel-Blocking Properties of Novel 10,11-Dihydro-5H-dibenz[b,f]azepine-5-carb oxamide Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, 1999, pages 2582-2587, XP002206156 ISSN: 0022-2623

D3: LEMKE MATTHIAS R: "Effect of carbamazepine on agitation in Alzheimer's inpatients refractory to neuroleptics" JOURNAL OF CLINICAL PSYCHIATRY, vol. 56, no. 8, 1995, pages 354-357, XP000903495 ISSN: 0160-6689

D4: FITZGERALD BRIAN J ET AL: "Elevation of carbamazepine-10,11-epoxide by quetiapine." PHARMACOTHERAPY, vol. 22, no. 11, November 2002 (2002-11), pages 1500-1503, XP009033502 ISSN: 0277-0008

D5: EP-A-0 751 129 (PORTELA & CA S A) 2 January 1997 (1997-01-02)

2.) The present application does not meet the criteria of Article 33(1) PCT, because the

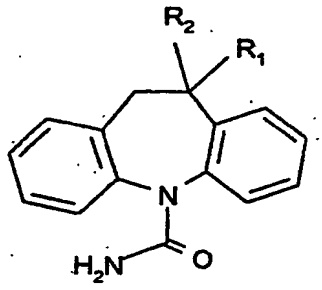
subject-matter of claims 1-12 does not involve an inventive step in the sense of Article 33(3) PCT.

Document D3 discloses the use of carbamazepin in the treatment of agitation. The mechanism may be related to GABAerg, serotonergic or dopaminergic properties. The subject matter of claim 1 differs in the change to compounds according to formula (I).
Document D1 discloses that oxcarbazepine affects the same systems as carbamazepine. It is especially mentioned that oxcarbazepine possesses a dopaminergic effect and that a serotonergic effect is likely.
Also, D2 shows that carbamazepine and oxcarbazepine exhibit the same binding.
Thus, taken the possible serotonergic and dopaminergic properties into consideration, the skilled person would expect that oxcarbazepine has, in the same way as carbamezepin, an effect in the treatment of agitation.
This is supported by D4 disclosing that oxcarbazepine can replace carbamazepine which had been administered for treating maladaptive behavior. Following this change, quetiapine induced agitation returned to baseline.

3.) For the assessment of the present claims 5-8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS

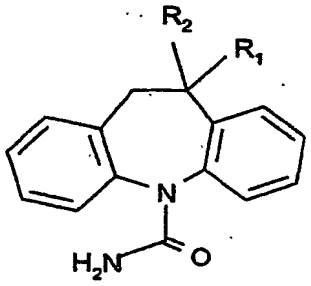
1. The use of a compound of formula I



(I)

wherein (a) R_1 and R_2 together form an oxy group or (b) R_1 is hydrogen and R_2 is hydroxy or acetoxy, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment of agitation.

2. The use of a compound of formula I



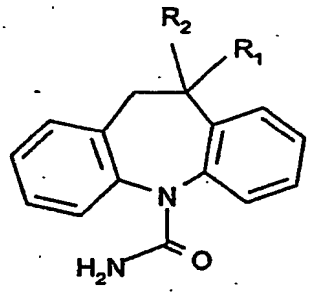
(I)

wherein (a) R_1 and R_2 together form an oxy group or (b) R_1 is hydrogen and R_2 is hydroxy or acetoxy, or a pharmaceutically acceptable salt thereof, for the treatment of agitation.

3. The use according to claim 1 or 2 wherein the disease is behavioral agitation.

4. The use according to any of claims 1 to 3, wherein the patient to be treated is diagnosed to have Alzheimer's disease.

5. A method for the treatment of agitation in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound of formula I



(I)

wherein (a) R_1 and R_2 together form an oxy group or (b) R_1 is hydrogen and R_2 is hydroxy or acetoxy,

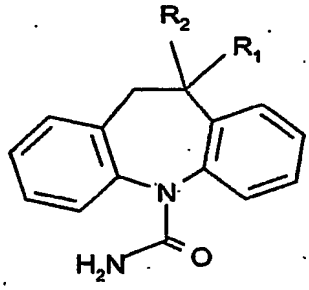
or a pharmaceutically acceptable salt thereof.

6. The method according to claim 5, wherein the compound of formula I is oxcarbazepine.

7. The method according to claim 5, wherein the disease is behavioral agitation.

8. The method according to claim 5, wherein the subject to be treated is diagnosed to have Alzheimer's disease.

9. A combination comprising (a) a compound of formula I



(I)

wherein (a) R_1 and R_2 together form an oxy group or (b) R_1 is hydrogen and R_2 is hydroxy or acetoxy,

and (b) at least one compound selected from the group consisting of nootropic plant extracts, calcium antagonists, cholinesterase inhibitors, dihydroergotoxin, nicergoline, piracetame, purine derivates, pyritinol, vincamine and vinpocetine, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier.

10. Combination according to claim 9, wherein the compound (b) is a cholinesterase inhibitor.

11. Use of a combination according to claim 9 or 10 for the preparation of a medicament for the treatment of agitation in dementia patients.

12. A commercial package comprising a combination according to claim 9 or 10 together with instructions for simultaneous, separate or sequential use thereof in the treatment of agitation in dementia patients.